REMARKS

In the Official Action dated April 30, 2004, claims 16-30 are pending and under consideration. Claims 16-20, 22, and 26-30 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by U. S. Patent 5,436,146 to Shenk et al. ("Shenk"). Claims 16 and 21 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shenk in view of Kim et al., *Cell* 42:129-138, 1985 ("Kim"). Claims 16 and 23 are rejected under 35 U.S .C. §103(a) as allegedly unpatentable over Shenk in view of U.S. Patent 5,326,700 to Berg et al. ("Berg"). Claims 24 and 25 are free of the prior art of record. The specification is objected to for allegedly failing to comply with the Sequence Rules. The Examiner has also requested a copy of the Decision on the Request for Reexamination, copies of the Summons and of the Dismissal Order of Avigen, Inc. v. Research Corporation Technologies, Inc., and a formal copy of the offer to surrender the original patent, U.S. Patent 6,261,834.

This response addresses each of the Examiner's objections and rejections. Accordingly, it is respectfully submitted that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

In the first instance, Applicant is providing herewith a copy of the Decision on the Request for Reexamination in Application No. 90/006,542, as well as copies of the Summons and of the Dismissal Order of the civil action, Avigen, Inc. v. Research Corporation Technologies, Inc. These documents were provided by Applicant in the paper mailed on July 16, 2003. Applicant is submitting these documents again as a courtesy to the Examiner.

Further, Applicant is providing herewith a formal copy of the offer to surrender the original patent, U.S. Patent 6,261,834, pursuant to 37 C.F.R. §1.178.

Regarding the objection to the specification, the Examiner states that the sequence that

appears in Figure 2 is not listed in the Sequence Listing.

Applicant respectfully submits that the sequence depicted in Figure 2 is set forth in SEQ ID NO: 2. Applicant has amended the specification to insert the sequence identifier in the drawing description for Figure 2. As such, the objection to the specification is overcome. Withdrawal of the objection is respectfully requested.

Claims 16-20, 22, and 26-30 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by U. S. Patent 5,436,146 to Shenk et al. ("Shenk").

The Examiner alleges that Shenk teaches a rAAV vector comprising only terminal AAV sequences and any foreign DNA sequence operably linked to a promoter (col. 5, line 67- col. 6, line 3 and col. 9, line 20- col. 10, lines 46). According to the Examiner, Shenk teaches that the rAAV vector retains only terminal AAV sequences that are necessary for integration, excision, replication, and packaging, and that comprise fewer than about 195 nucleotides of the AAV terminus (col. 9, lines 31-34). The Examiner also refers to col. 10, 14, and 15, where Shenk allegedly teaches using 191 bp segments from the termini of psub201, a vector which comprises AAV-2 DNA. The Examiner notes that psub201 was also used by Applicant to obtain the AAV-ITRs, as described in the specification. Furthermore, referring to col. 9, line 63 to col. 10, line 46, the Examiner alleges that Shenk teaches using a tissue specific promoter in the vector.

Applicant respectfully submits that the claims have been amended to more clearly delineate preferred embodiments of the present invention. Specifically, claim 1 has been amended to recite "wherein each of said inverted terminal repeats is SEQ ID NO: 1 or a fragment of SEQ ID NO: 1 that comprises nucleotides 1 to 125 of SEQ ID NO: 1." Support for such amendment is found in the specification, e.g., on col. 9, lines 41-45, where the text

refers to "the 145 nucleotides of FIG. 1" (i.e., SEQ ID NO: 1) and "[f]ragments which contain the 125 nucleotides which form the palindromic hairpin (nucleotide 1-125 of FIG. 1)" (i.e., nucleotide 1-125 of SEQ ID NO: 1). No new matter is added.

Applicant respectfully submits that Shenk does not teach a rAAV-2 vector, as presently claimed. Specifically, Shenk does not teach a recombinant AAV-2 vector, wherein each of the terminal repeats is SEQ ID NO: 1 or a fragment thereof that comprises nucleotides 1-125 of SEQ ID NO: 1. It is recognized that Shenk teaches the following with respect to ITRs:

> "[T]he the rAAV vector retains only terminal AAV sequences necessary for integration, excision, replication, and packaging; *comprising less than about* 195 base pairs of the AAV terminus. In a specific embodiment of the invention, recombinant viruses were generated that contained only 191 nucleotides of the AAV chromosome, and were derived from plasmid psub201 DNA, ..." (Emphasis added.)

See, col. 9, lines 30-37 of Shenk.

Applicant respectfully submits that the language "comprising less than about 195 bases of the AAV terminus" in Shenk does not constitute adequate teaching that would anticipate the presently claimed vector. The only specific fragment that is shorter than 195 bp, disclosed by Shenk, is a 191bp fragment. Contrary to the present application, there is no recognition by Shenk that a shorter fragment of the AAV terminus, as presently claimed, would retain the sequences necessary for integration, replication, and packaging of the recombinant virion.

Applicant further respectfully submits that the instant rAAV vectors containing shorter ITR fragments are advantageous over other rAAV vectors, such as Shenk's vector containing 191-bp ITR fragments. Because the wild type AAV is 4.68 kb long, the heterologous DNA insert size is limited in order to have successful and efficient packaging of the recombinant

virion. The instant rAAV vectors, which have ITR sequences that are shorter than those taught in Shenk by 92 base pairs or more, certainly permit more flexibility in incorporating heterologous sequences in the vector.

Moreover, Applicant respectfully submits that Shenk does not adequately teaches a rAAV vector comprising a cell-specific promoter that achieves expression of a heterologous gene in a cell-specific manner. The only teaching in Shenk with respect to promoters having tissue specificity comes in the form of a laundry list of tissue specific promoters on col. 10, without providing showing of tissue specific expression.

Accordingly, Applicant respectfully submits that Shenk does not provide adequate teaching that would anticipate the vectors as presently claimed. Therefore, the rejection of claims 16-20, 22, and 26-30 under 35 U.S.C. §102(e) based on Shenk is overcome. Withdrawal of the rejection is respectfully requested.

Claims 16 and 21 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shenk in view of Kim et al., *Cell* 42:129-138, 1985 ("Kim").

The Examiner concedes that Shenk does not specifically teach using the heterologous gene encoding an antisense RNA in the rAAV vector. However, the Examiner contends that at the time the invention was made, Kim teaches reducing thymidine kinase activity in mouse cells *in vitro* using anti-sense thymidine kinase gene. Therefore, the Examiner concludes that the vector as claimed in claims 16 and 21 is obvious in view of Shenk taken with Kim.

Applicant respectfully submits that Shenk, the primary reference, does not teach or suggest the rAAV vector as presently claimed, wherein each of the inverted terminal repeats in the vector is SEQ ID NO: 1 or a fragment of SEQ ID NO: 1 that comprises nucleotides 1 to 125 of SEQ ID NO: 1. Further, those skilled in the art would not have had a reasonable

expectation that a vector, as presently claimed, would retain the capacity of integration, replication, and packaging of the recombinant virion. Applicant further respectfully submits that Kim does not cure the deficiencies of Shenk. The cited references, taken alone or in combination, simply do not teach or suggest the vectors as presently claimed. Therefore, the rejection of claims 16 and 21 under 35 U.S.C. §103(a) based on Shenk and Kim is overcome. Withdrawal of the rejection is respectfully requested.

Claims 16 and 23 are rejected under 35 U.S .C. §103(a) as allegedly unpatentable over Shenk in view of U.S. Patent 5,326,700 to Berg et al. ("Berg").

The Examiner admits that Shenk does not specifically teach using the heterologous gene encoding P-glycoprotein in the rAAV vector. However, the Examiner contends that, at the time the invention was made, Berg teaches introducing a gene encoding a P-glycoprotein into a cell line and using it as an amplifiable marker (col. 10, lines 13-27). Therefore, the Examiner concludes that the vector as claimed in claims 16 and 23 is obvious in view of Shenk taken with Berg.

As submitted above, Shenk does not teach or suggest the rAAV vector as presently claimed, wherein each of the inverted terminal repeats in the vector is SEQ ID NO: 1 or a fragment of SEQ ID NO: 1 that comprises nucleotides 1 to 125 of SEQ ID NO: 1. Further, those skilled in the art would not have had a reasonable expectation of success in arriving at the invention as presently claimed. Similar to Kim, Berg does not cure the deficiencies of Shenk. The cited references, taken alone or in combination, simply do not teach or suggest the vectors as presently claimed. Therefore, the rejection of claims 16 and 23 under 35 U.S.C. §103(a) based on Shenk and Berg is overcome. Withdrawal of the rejection is respectfully requested.

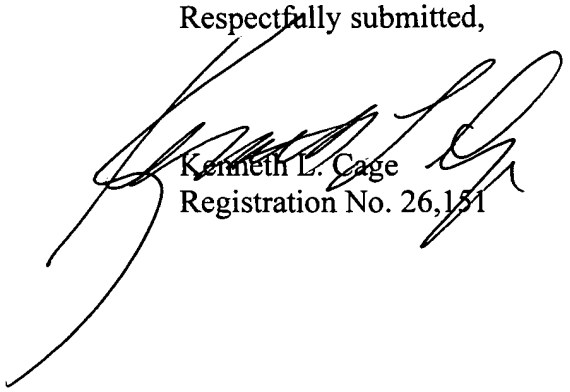
To ensure that all issues material to the patentability of the pending reissue claims are presented, Applicant notes that, in newly presented claims 16-23, the preamble expression "*for site specific integration and cell specific integration,*" appearing in originally issued claim 1, '834 Patent, C. 1, ll. 37-38, is not included. See, Arun Srivastava's "Declaration In Support of Reissue Under 37 C.F.R. §§ 1.175 and 1.63." In determining that originally issued claim 1 was allowable and non-obvious, the Board of Patent Appeals & Interferences ("Board") agreed with Appellant :

> "Lebkowski et al. states that "theoretically, all sequences between the two AAV inverted terminal repeats can be deleted and replaced with endogenous DNA" [appellant's emphasis]. Lebkowski et al., however, does not teach, or even suggest, that all sequences between the two AAV terminal repeats can be deleted and replaced by endogenous DNA to construct a vector capable of site specific integration and cell specific expression [appellant's emphasis]. It is only with the benefit of the present specification that the Examiner establishes a nexus between the claimed invention and the cited prior art teaching. Brief , p. 6., " P. 10, l. 21 to p. 11, l. 8.

In this regard, Applicant does not believe the recapture rule enunciated in *Hester Industries, Inc. v. Stein*, 142 F. 3d 1472, 46 U.S. P.Q. 2d 1641 (Fed. Cir. 1998) applies to the present facts because, *inter alia*, the term deleted from the claim is a preamble term.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Copy of the Decision on the Request for Reexam;
Copy of the Summons of Avigen v. RCT;
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